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Intra-Operative Radiation Therapy in Pediatric Neuroblastoma

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External beam irradiation (EBRT) has been shown to improve response rates and event-free survival in children with neuroblastoma and regional lymph node metastases. Irradiation during surgical exposure (intra-operative radiotherapy, IORT) with displacement of adjacent radiosensitive organs out of the treatment field allows for more precise delineation of the target volume and significantly reduces the amount of normal tissue exposed to irradiation. We have incorporated IORT into the treatment regimen of 24 children with neuroblastoma between the years 1983–1991. IORT was directed to any residual tumor or the tumor bed; the median dose of radiation was 1,000 cGY, equivalent to 3,000 cGY of conventional EBRT. There were 11 males and 13 females. Two patients had stage II, 12 patients had stage III, and 10 patients had stage IV disease. Ten children received IORT for suspected recurrent or persistent neuroblastoma.

Twelve patients were disease-free survivors following IORT with a median follow-up of 54 months. For those patients with stage III disease, seven children were disease-free survivors, while only three of 10 patients with stage IV disease survived (median follow-up 30 months). Disease-free Survival (DFS) correlated with the achievement of local tumor control in children with both stage III and IV neuroblastoma. There was limited morbidity and no episodes of obstructive uropathy were encountered. We conclude that IORT appears to be well tolerated and may have therapeutic benefit for a select group of patients with neuroblastoma. IORT merits future exploration by prospective study. Med. Pediatr. Oncol. 28:424–428, 1997.

Key words: neuroblastoma; radiotherapy; child; intra-operative radiotherapy

INTRODUCTION

Neuroblastoma is the second most common solid tumor of childhood [1]. Important prognostic variables include age at diagnosis, tumor stage, primary site, DNA ploidy and amplification of the N-myc oncogene in the tumor tissue [2–6]. Survival in advanced disease, despite surgical resection and the use of adjuvant chemotherapy, has remained poor [1].

Conventional external beam radiation therapy (EBRT) delivered to local neuroblastoma tumor sites has several well-recognized applications. In relieving respiratory distress for infants with stage IVS neuroblastoma, relatively low dose radiation therapy to the liver has been effective [7]. EBRT has been shown to improve response rates and event-free survival in children with regional lymph node metastases [8]. EBRT is widely used in advanced stage neuroblastoma to sites of originally bulky disease as an adjuvant to surgery and chemotherapy and as an adjuvant to myeloablative chemotherapy and bone marrow transplant [9,10]. In other clinical settings, the role of radiation therapy is less well established. For patients with stage II neuroblastoma who have had a surgical resection of the primary tumor, treatment with adjuvant therapy has recently been questioned. In this setting, radiation therapy may not be indicated even in the presence of residual disease [11–13].

Intra-operative radiotherapy (IORT) is a method by which a single large dose of irradiation is delivered to the tumor bed, to a precisely defined volume and depth of tissue penetration, in an effort to maximize the tumoricidal radiation effect while attempting to avoid unnecessary dose-limiting side effects to normal tissues [14–19]. This retrospective analysis reports the results of IORT in 24 children with neuroblastoma treated over a 9-year period at a single institution.

METHODS

We retrospectively reviewed the case histories of 24 consecutive children with neuroblastoma treated with IORT between the years 1983–1991. This represents 29% (24 of 82) of the total referrals of children with neuroblastoma to our institution over the same time period. The International Neuroblastoma Staging System (INSS) and Evans staging were determined for this study

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by retrospective interpretation of clinical, radiological and surgical data. Information regarding Shimada classification was recorded by chart review and by blinded histopathological review of pathology specimens where available. N-myc copy number was recorded by chart review when available. Appropriate informed consent was obtained for IORT by the surgeon and radiation oncologist. Each surgical procedure was planned with an intent to completely resect the tumor. Extent of the surgical resection was determined by the primary surgeon and was not dependent on radiological imaging or pathological interpretation of the resection margin. These data were confirmed later by secondary evaluation by the Children's Cancer Group (CCG) study surgeon. IORT was directed to any gross residual tumor or to the tumor bed with minimal margins. Electron beam IORT was delivered through lucite cylindrical ''cones,'' 3 cm to 7.5 cm in diameter, constructed with sufficient wall thickness to contain the beam energy within the boundary of the cylinder. Electrons, unlike photon (x-ray) irradiation, are easily attenuated in matter which allows for sharp fall-off of irradiation dose at depth in tissue. By placing the cone directly on the target tissue during surgical exposure, a precise treatment area is delineated and visual confirmation of the exclusion of adjacent organs, e.g., bowel or ureter, can be obtained. The median dose of radiation was 1,000 cGY(700–1,500 cGY), given with an electron beam of 5–11 MeV. Beam energies of 5 to 11 MeV were used, to limit the intended radiation dose to 1 to 4 cm depth, depending upon the target thickness. The lower dose and energy ranges were designed for the ''pseudocapsule'' bed or areas of ''microscopic'' disease and the higher ranges for gross residual disease. This single dose is considered equivalent to 2,500–3,000 cGY of conventionally fractionated EBRT. Doses of 700 cGY to 1,500 cGy were given in a single session. The cytocidal effect of a single large exposure is quantitatively 2–3 times greater than the same numerical total dose given in multiple fractions over time. This is due to the cell repopulation during the interfraction intervals and more complete DNA damage repair at lower doses, rendering more of the total given dose ''sub-lethal.''

RESULTS

Between 1983–1991, we treated 24 patients with neuroblastoma with adjuvant IORT, in addition to other standard therapy. The age range for this group was between 4 and 80 months (median 22 months) at diagnosis and the age range was between 7 and 84 months (median 27 months) at time of IORT. All had the surgical procedure and IORT in one institution. Ninety-two percent (n = 22) were treated with varying chemotherapy regimens and 25% (n = 6) had additional external beam radiation. Fourteen children had IORT as part of the initial therapeutic approach while ten children were treated for suspected recurrent disease (n = 8), or persistent disease (n = 2) despite combination therapy. There were 11 males and 13 females, two patients with stage II, 12 patients with stage III and ten patients with stage IV disease at initial diagnosis by Evan's stage (Table I). Both patients with stage II neuroblastoma had primary posterior mediastinal disease, while 18 of 22 patients with stage III and stage IV neuroblastoma had abdominal primaries.

IORT was delivered during a primary surgical procedure in 14 of 24 children. Of these 14 children, five had a complete gross surgical excision. A complete gross surgical resection was achieved in four of 10 patients who received IORT during a second surgical procedure of whom eight had stage III disease (Table I). Patients who required a second surgical procedure had recurrent disease or were referred to our institution after having incomplete surgical procedures performed at another center. While four patients had complete gross tumor resection at the time of the second operation, three of these did not have viable disease on histopathologic examination (patients 1, 23 and 9). One of these children (patient 23) with stage IV neuroblastoma had persistent hypertension after the primary operation. With the expectation of residual disease, a second operation was performed in this patient, during which IORT was given. One further patient (13) was diagnosed with recurrent disease after viable neuroblastoma cells were visible in resected retroperitoneal lymph nodes during a diagnostic procedure. Chemotherapy was administered during the interval between this operation and the definitive procedure during which IORT was given. Resected specimens from the definitive operation did not have any viable tumor. Two patients who had stage III neuroblastoma at diagnosis had visible metastatic disease by the time a second operation was required during which IORT was administered (patients 5 and 14).

Pathological criteria relating to Shimada classification [4] were available in 12 patients, while N-myc copy number was available in nine (Table I). One patient with stage II neuroblastoma had favorable histology and no amplification of the N-myc oncogene. Histopathological data relating to Shimada classification were available in seven children with stage III disease, of whom four had unfavorable criteria. Three of 12 patients with stage III neuroblastoma had N-myc copy number results available and only one of these three showed oncogene amplification (also with unfavorable Shimada). Histopathological data relating to Shimada classification were available in four of 10 patients with stage IV neuroblastoma, three of whom had unfavorable criteria. Of five stage IV children with N-myc studies, one child had amplified N-myc gene copy number (also with unfavorable Shimada).

There was no recurrence of disease in the IORT field in 13 of 24 patients with a median follow-up of 4.5 years (range 18–96 months). Four of these patients had no viable tumor seen at the time of IORT administration.

TABLE I. Patient Summary

Patient number	Age at diagnosis (Months)	Evans stage at diagnosis	INSS[b] stage at diagnosis	Shimada classification Favorable (F)/ Unfavorable (U)	N-myc oncogene copy no.	Viable tumor in resected specimen (Y or N)	Time of operation with IORT Primary (P)/ Secondary (S)	Survival status Alive (A)[c]/ Dead (D)	Follow-up duration (Months)
1	9	II	2B	F	1	N	S	A	47
2	66	II	1	NA[a]	NA	Y	P	A	77
3	24	III	3	F	3	Y	S	A	72
4	14	III	3	NA	NA	Y	P	A	70
5	36	III	3	NA	NA	Y	S	D	28
6	12	III	3	U	NA	Y	P	D	9
7	5	III	3	F	NA	Y	P	A	84
8	21	III	3	U	45	Y	S	D	24
9	10	III	3	F	NA	N	S	A	36
10	9	III	3	NA	NA	Y	P	A	96
11	60	III	3	NA	NA	Y	S	D	22
12	14	III	2A	NA	1	Y	S	A	22
13	7	III	3	U	NA	N	S	A	60
14	35	III	3	U	NA	Y	S	D	19
15	80	IV	4	U	1	Y	P	D	15
16	40	IV	4	U	1	Y	P	A	18
17	29	IV	4	NA	NA	Y	P	D	14
18	23	IV	4	U	35	Y	P	D	10
19	36	IV	4	NA	NA	Y	P	A	30
20	5	IV	4	NA	NA	Y	P	D	7
21	20	IV	4	NA	NA	Y	P	D	6
22	48	IV	4	NA	NA	Y	P	D	36
23	26	IV	4	NA	1	N	S	D	38
24	4	IV	4	F	1	Y	P	A	48

[a]NA, not available for review and not defined in original surgical or pathology report.
[b]INSS, International Neuroblastoma Staging System.
[c]Alive, all children alive at the time of review were without evidence of disease.

The patients with stage II neuroblastoma are both alive at 77 and 44 months. One patient with stage III neuroblastoma, after a complete gross surgical resection during a primary surgical procedure, remains alive at 96 months. Two patients also with stage III disease, despite residual disease after an incomplete primary resection and having received no subsequent therapy other than IORT, are also alive at 70 and 84 months. Of eight patients with stage III disease who had IORT during a second operation, four are without local disease recurrence at 22, 36, 60 and 72 months. Two of these four patients remain disease-free despite residual disease after an incomplete resection at the time of IORT. Thus, therapy which incorporated IORT achieved local tumor control in four patients with stage III neuroblastoma, despite macroscopic residual disease after surgical resection. Four patients with stage IV disease had no local disease recurrence. One of these four died from an aspergillus pneumonia but had no evidence of disease within the IORT field at postmortem 38 months post-IORT. This patient did, however, have distant metastatic disease.

The overall disease-free survival (DFS) following IORT was 12 of 24 children, with a follow-up 18 to 96 months (median 54 months). There were seven patients under the age of 12 months when IORT was administered (three during a second surgical procedure) and only one of these seven has died. The DFS for patients with stage III disease was seven of 12 patients. For those patients with stage III neuroblastoma who had IORT during a second procedure, the DFS was four of eight. Three children with stage IV neuroblastoma have survived with a median follow-up of 30 months.

IORT was tolerated well by patients in this study group. Complications included transient mild pancreatitis in one patient whose radiation field included the pancreas, liver and renal bed. Two patients developed postoperative intussuception. One child required a laminectomy (T8-L3), at the age of 8 months, to remove a paraspinal neuroblastoma, and developed scoliosis although she did not receive external beam radiation therapy. One patient had a preoperative obstructive uropathy which has persisted but no patients developed de novo postoperative obstructive urological sequelae. Although many patients received IORT to paraspinous fields, no neuropathies have been seen. So far there have been no long-term sequelae attributable to IORT.

DISCUSSION

IORT has been demonstrated to have an impact on local tumor control in a variety of adult cancers [20–22]. In pediatrics, IORT is less well defined as a beneficial adjuvant to standard therapy. Recently IORT has been

described in a cohort of pediatric patients with varying benign conditions and malignancies [18]. In this report we have been able to evaluate the impact of IORT in 24 of 82 children (30%) diagnosed with neuroblastoma over a 9-year period. IORT was used when there was gross or microscopic residual disease or if the original tumor bed margins were not adequately clear, as determined by the surgeon [18]. Those children who did not receive this therapeutic modality during the study period were treated with standard therapeutic protocols. With longer follow-up for neuroblastoma patients in this report than previously described [18], we suggest that IORT is tolerable in a pediatric population and may have a role in the treatment of neuroblastoma in a subset of patients. Neuroblastoma already has several well-recognized prognostic factors and the outcome of this small patient cohort conforms to the expected outcome when related to prognostic factors such as age at diagnosis [23] amplification of the N-myc oncogene [5] and the Shimada classification of diagnostic tissue [4,24]. We have data relating to the Shimada classification in 12 patients (Table I). No initial diagnostic tissue was retrievable for evaluation in 10 patients. Fine needle aspiration was used for diagnosis in two patients and was therefore not interpretable for Shimada classification. When material was available for review, there was no difference from the original histopathological interpretation. The outcome for the patients reported in this study does relate to the histopathological characteristics at diagnosis with only two children with unfavorable Shimada classification surviving. Amplification of the N-myc oncogene was also related to poor outcome since both patients with amplified copies (>10 copies) relapsed and died while five patients (71%) with nonamplified copies remain alive and disease-free (median follow-up 47 months). Both patients with nonamplified N-myc who died had stage IV neuroblastoma. Although there were seven children treated with IORT who were under 1 year at diagnosis, three were treated during a second surgical procedure and two others had stage IV disease.

Complications relating to the delivery of radiation therapy are dependent on the dose of radiation given and on volume and the sensitivity of the organs in the radiation field [25]. In this pediatric population, there was limited morbidity in response to the administration of IORT. No episodes of obstructive uropathy followed IORT [26] as circumferential coverage of the ureter was avoided. One child, who did not receive external beam radiation therapy, has residual scoliosis after laminectomy and IORT. Because of such late sequelae of laminectomy without irradiation in growing children, this procedure has been replaced by osteoplastic laminotomy in this clinical situation [27,28]. There were no other toxicities [16,17] related to radiation therapy.

Neuroblastoma can recur either locally or with distant metastasis. The recurrence rate is maximal during the first year after therapy and late recurrences after 5 years are very rare [29,30]. In this report, the median follow-up is 4.5 years (9 to 96 months). Survival statistics vary for different stage disease, with cure rates $\geq$90% for stage I + II [31]. Children with stage II disease may not actually require therapy other than surgery even when the surgical procedure is not complete [11–13]. Both children with stage II disease in this report are alive. The indication for IORT in one of the two patients was suspected recurrent disease. IORT was well tolerated by both. Stage III survival statistics range from 63% to 81% [16,31,32]. In our study, seven of 12 patients (58%) with stage III disease are alive and have had no recurrence of disease within the IORT field (follow-up 9 to 96 months, median 36 months from diagnosis). Rosen et al. [16], who reported survival rates of 81% for children with stage III neuroblastoma treated with surgery, conventional radiation and chemotherapy, explains these survival figures by the use of intensive multimodality therapy. Given that there were two patients in our study with stage III neuroblastoma at diagnosis who had clearly evident metastatic disease at the time of a second surgical procedure, the DFS we report is an encouraging outcome. In the current report, four of 12 children (33%) with stage III disease were less than 1 year of age at diagnosis, while 56% of those with stage III neuroblastoma were less than 1 year at diagnosis in the report by Rosen et al. [16]. Disease-free survival in eight patients with stage III disease who had IORT administered during a second operation to completely resect the primary tumor was four of eight. Two patients in this latter group are disease-free despite an incomplete resection during the second operation during which IORT was given. Thus, four children with stage III neuroblastoma who had an incomplete surgical resection and IORT achieved local disease control. This suggests that IORT may have an important adjuvant role in achieving local tumor control, in this patient group. While patients with stage IV disease have a very poor chance of survival [31], we report local tumor control in four children with stage IV neuroblastoma. This is satisfactory recognizing that 50% of the children with stage IV neuroblastoma were diagnosed before 1988 and had less intense adjuvant chemotherapy compared to those diagnosed later. However, only three of 10 children with stage IV disease survived; thus, the likelihood of benefit from IORT in stage IV neuroblastoma is unresolved.

CONCLUSIONS

Our results suggest that children with stage III neuroblastoma may benefit from the use of IORT during either the primary or secondary surgical procedure. We conclude that IORT at these doses appears to well tolerated, may have therapeutic benefit for a select group of pa-

tients with neuroblastoma and is deserving of additional prospective trial in a larger number of patients.

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